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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Shin-ichi Hashimoto

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08/05/2008

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EXAMINER

MEAH, MOHAMMAD Y

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/590,705	Applicant(s) HASHIMOTO ET AL.	
	Examiner MD. YOUNUS MEAH	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 16-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/25/06, 11/29/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' election with traverse of group I (claims 1-15) in their response of 05/05/2008 is acknowledged.

Election/Restriction

Applicant, on date 05/05/2008, elected without traverse Group I (claims 1-15); drawn to method of production of amino acid using microorganism expressing energy non-producing NADH dehydrogenase of SEQ ID NO: 4 for examination. Groups II-XIV of election/restriction-office action of date 04/7/2008 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups.

Applicants' argument that groups I-VI should be examined together because they comprise single inventive concepts and share common technical feature is not found persuasive because these groups comprise method steps involving different proteins having different SEQ ID NOs, hence different structure. As explained in the election restriction, each DNA or protein having unique SEQ ID NO is different DNA or protein having unique structure and comprise special technical feature. Therefore the restriction is maintained and made FINAL.

Priority

Acknowledgement is made of applicants' PCT application PCT/JP05/03694 filed 02/25/2005 and foreign application Japan 2004-053361 filed 02/27/2004.

Objections

Claims 1-5, 7-13 are objected in the recitation "DNA coding for". The term "DNA coding for" should be replaced by the term "DNA encoding". Appropriate correction is required.

Claim 5 and 7 are objected in the recitation "possessed by" and "carried by" they should be replaced by "within". Appropriate correction is required.

Claim 5 and 7 are objected in the recitation in line 2 "a DNA" and in line 3 "a plasmid" they should be replaced by "the DNA" and "the plasmid". Appropriate correction is required.

Claim Rejections

35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims, 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

Claims 1-15, the recitation "energy non-production" makes the claim unclear. What does the energy non-production mean? Specification teaches that said NADH dehydrogenase yields net 0 electron in the oxidation-reduction

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reaction. However it is unclear what is the relation between energy non-production and 0 electron production.

Claim 1 line 2, the recitation “ microorganism obtainable by introducing a DNA coding for ” makes the claims unclear. It is suggested to replace the term “microorganism obtainable by introducing a DNA coding for ” by the term “microorganism expressing a heterologous DNA encoding”

Claims 2-5 are indefinite in the recitation of “stringent conditions” as the specification does not define what conditions constitute “stringent”. While page 17 of the specification describes some conditions, which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a gene encoding SEQ ID NO: 4, a sequence must be to be included within the scope of these claims.

35 U.S.C 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-15 are rejected under 35 U.S.C. 112, first paragraph, as

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containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 6-15 are directed to a method of production of amino acid by using a microorganism expressing any heterologous DNA encoding energy non-producing NADH dehydrogenase having any structure (claims 1-3, 6-15) or any DNA which hybridize with SEQ ID NO: 3 or any DNA encoding any variant of SEQ ID NO: 4 having any number of amino acid variation. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches method of production of amino acid by using a microorganism expressing only a few heterologous DNA encoding energy non-producing NADH dehydrogenases (SEQ ID NOs: 4,6,8,10,12,14 and 16). Moreover, the specification fails to describe any other representative species by

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sufficient identifying characteristics or properties to show that applicant was in possession of the claimed genus.

There is no structure-function correlation with regard to the members of the genus of polypeptide molecule reciting energy non-producing NADH

dehydrogenase having any structure claimed in the instant claims 1-3, 6, 8-15.

The specification discloses the structure of a few energy non-producing NADH dehydrogenases. Therefore one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Applicants' are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of production of amino acid by using a microorganism expressing heterologous DNA of SEQ ID NOs: 3, 5, 7, 9, 11, 13 or 15 encoding energy non-producing NADH dehydrogenase of SEQ ID NOs: 4, 6, 8, 10, 12, 14 and 16, does not reasonably provide enablement for method of production of amino acid by using a microorganism expressing any heterologous DNA encoding any energy non-producing NADH dehydrogenase having any structure (claims 1-3, 6, 8-15) or any DNA which hybridize with SEQ ID NO: 3 (claims 4 and 5) or any DNA encoding any variant of SEQ ID NO: 4 having any number of amino acid variations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

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nearly connected, to make the invention commensurate in scope with these claims.

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP § 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 1-15 encompass a microorganism expressing any heterologous DNA encoding energy non-producing NADH dehydrogenase having any structure (claims 1-3, 6, 8-15) or any DNA which

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hybridize with SEQ ID NO: 3 or any DNA encoding any variant of SEQ ID NO: 4 having any number of amino acid variation.

The state of the prior art; The relative skill of those in the art; and The predictability or unpredictability of the art: It is well known in the prior art that the amino acid sequence of a protein determines the protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired dehydrogenase activity requires knowledge and guidance regarding specific amino acid residue(s) in the protein's amino acid sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and detailed knowledge of the protein's structure, and the ways in which the protein's structure relates to its function. The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug; 16(4):378-84; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships.

The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired dehydrogenase activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with

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each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Methods for isolating or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the amino acid sequence of any energy non-producing NADH dehydrogenase to obtain desired dehydrogenase activity or for altering the amino acid sequence of SEQ ID NO: 4 with an expectation of obtaining a polypeptide having the same activity. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the same desired biological activity. For example, the reference of Witkowski et al. (Biochemistry. 1999 Sep 7; 38(36): 11643-50; PTO 892) teaches that only a single amino acid substitution results in conversion of the activity of a polypeptide to a second, distinct activity (see e.g., Table 1, page 11647). In addition, the reference of Seffernick et al. (J Bacteriol. 2001 Apr; 183 (8): 2405-10; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrazine chlorohydrolase activity (see Fig.3, page 2408; **DISCUSSION** section on page 2409).

The amount of direction provided by the inventor; and the existence of working examples: Claims 1-3, 8-15 recite energy non-producing NADH dehydrogenase having any structure. Claims 4 and 5 recite any DNA encoding

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an energy non-producing NADH dehydrogenase which hybridize with SE ID NO: 3 under any stringent conditions. The specification disclose a few working examples of such energy non-producing NADH dehydrogenase. However, the specification fails to disclose any specific guidance for altering the amino acid sequence of any energy non-producing NADH dehydrogenase with expectation that the polypeptide will still have the same dehydrogenase activity, because guidance and working examples teaching unalterable structural and catalytic amino acid residues and amino acid residues tolerable to change is not provided by the specification.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a polypeptide were known in the art at the time of the invention and the specification provides general teachings for searching and screening for the claimed invention, it was not routine in the art to screen by a trial and error process for all polypeptides having a substantial number of modifications as encompassed by the claim(s) for those that maintain the same desired dehydrogenase activity. General teachings from the specification regarding screening and searching for the claimed invention using enzyme assays is not specific guidance for making and using the claimed invention.

Therefore, in view of the overly broad scope of the claims, the specification's lack of specific guidance and additional working examples, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, it would require undue experimentation for a skilled

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artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)).

Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)).

Claims 5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 5 and 7 recite a novel plasmid containing novel sequences. Since the plasmid is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids' sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the plasmid. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of plasmid should have been made in accordance with 37 CFR 1.801-1.809.

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It is noted that applicants have deposited the organisms but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
4. the deposit will be replaced if it should ever become inviable.

CLAIM Rejection - 35 U.S.C 103a

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made

Claims 1-15 are rejected under 35 U.S.C. 103(a) by Bott et al (J. Biotechnol, 2003, 129-153, from IDS) in view of Nakagawa et al. (US20020197605).

Claims 1-15 are directed to the method of production of amino acid by using various microorganisms (including *E.coli*, *Corynebacterium*) expressing DNA encoding any energy non-producing NADH dehydrogenase or DNA of SEQ ID NO: 3 encoding energy non-producing NADH dehydrogenase of SEQ ID NO: 4.

Bott et al describes the production of amino acids by *Corynebacterium glutamicum* and also, describes that respiratory chain enzymes involved in the oxidative phosphorylation in the aerobic respiration of *Corynebacterium glutamicum* are useful in amino-acid production and one such enzyme is NADH dehydrogenase. *Corynebacterium glutamicum* only contain energy non-producing NADH dehydrogenase, (Nantapong et al. Biosci, biochem, 2005, 69, 149-159, page 150, 1st paragraph, From IDS). Bott et al do not teach the method of

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producing amino acid by using microorganism transformed with heterologous NADH dehydrogenase derived from *Corynebacterium glutamicum*.

Nakagawa et al. teach NADH gene of SEQ ID NO: 1 isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3.

It is well known in art how to introduce and express the gene in a proper host. Therefore one knowledgeable in prior art is motivated to express *E. coli* with energy non-producing NADH gene of SEQ ID NO: 1 (taught by Nakagawa et al.) and use the said transformed microorganism in the method of production of amino acid.

As such it would have been obvious to one of ordinary skill in the art to use Nakagawa et al. NADH gene of SEQ ID NO: 1 isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3 express the said gene in *E. coli* and use the transformed *E. coli* to the method of production of amino acid as taught by Bott et al..

Furthermore, as Bott et al describes the production of amino acids by *Corynebacterium glutamicum*, in order to further enhance the production of amino acids by *Corynebacterium*, one ordinary skill in the art is motivated to express heterologous NADH dehydrogenase gene of SEQ ID NO: 1 (Nakagawa et al.) in *Corynebacterium*. One of ordinary skill in the art would reasonably expect this to increase the amount of the NADH dehydrogenase produced in the *Corynebacterium* and to therefore, enhance the amino acid production..

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As such it would have been obvious to one of ordinary skill in the art to use Nakagawa et al. NADH dehydrogenase gene of SEQ ID NO: 1 isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3 express the said gene in *corynebacterium* and use the transformed *corynebacterium* to the method of production of amino acid as taught by Bott et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR

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system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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